REMARKS

Claims 14, 17, 19, 29, and 38-41 are pending. Applicants have cancelled claims 1-13, 15, 16, 18, 20-28, and 30-37 and reserve the right to pursue the subject matter of these claims separately. Claims 14, 17, 19, 29, 38, and 40 have been amended herein; the amendments do not introduce any new matter to the pending claims.

Rejection of Claims 12, 14, 17, 19, 29, and 36-41 Under 35 U.S.C. § 112, First Paragraph

Claims 12, 14, 17, 19, 29, 36-41 stand rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement.

The Examiner has stated the issue as "whether these assays would be predictive in the ways that applicants' claims suggest" and that the specification does not provide ample evidence to support the claims. Applicants respectfully traverse and maintain that the specification does provide evidence of a clear association with predictive value for the following reasons.

First, Applicants draw the Examiner's attention to the preamble of the claims before the current amendment, which was directed to a method of predicting the likelihood of development of a metastatic condition. The claims did not require an absolute predictive value, that is, for example, if a higher level of a gene product recited in the claims is detected in a patient's sample, the patient *will* develop a metastatic condition. Instead, the claims required a relative predictive value, that is, if a higher level of a gene product recited in the claims is detected in a patient's sample, the patient *will more likely than not, or be at an increased risk to*, develop a metastatic condition. In other words, the claimed methods were directed to evaluating a risk factor of development of a metastatic condition, but not to predicting with absolute certainty that a patient will or will not develop a metastatic condition. Applicants believe that the preamble before the current amendment conveyed that. However, to expedite prosecution, Applicants have amended the preamble to recite "a method of evaluating the risk of development of a metastatic condition . . . ," which more clearly points to the relative predictive value of the claimed methods.

Having established that the claimed methods are directed to evaluating a risk factor instead of ascertaining an outcome, Applicants respectfully submit that the specification

provides ample support for the pending claims. The claimed method is based on a correlation of the level of certain gene products with the level of risk for metastasis, and the correlation has been adequately taught by the specification with numerous specific gene product examples.

The specification teaches numerous specific gene product examples. Applicants obtained the data regarding these gene product examples using highly sensitive and reliable mRNA microarray and RNAse protection technologies and analyzed the data with great rigor. To illustrate, the specification provides,

> For a gene to be selected as induced as described herein, it has to be expressed in all three metastatic samples (either M1, M2, and SM or F1, F2, and F3) at least 2.5-fold higher than in the poorly metastatic sample (either P or F0), done in duplicate. Where expression in the poorly metastatic sample was below baseline (arbitrarily set at 20, the point below which changes in expression could be determined with high confidence), it was determined to be absent and was set to 20. Reproducibility experiments were used to define the 2.5-fold expression threshold; at this threshold a 0.04% false positive rate (one false positive in 2500 genes) was achieved for a duplicate sample.

Page 26, lines 13-21 of the specification. Accordingly, Applicants respectfully submit that the specification as filed provides highly accurate correlation data on the numerous specific gene products.

Applicants also submitted post-filing date references as a confirmation as to the accuracy of the correlation data in the specification as filed. With respect to such post-filing date evidence, the Federal Circuit, in *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995), held that such evidence, although not "render[ing] an insufficient disclosure enabling," can be used "to prove that the disclosure was in fact enabling when filed . . . ." The references submitted by Applicants are merely to confirm what was already disclosed in the present application as filed, not to add anything new or cure any insufficiency. Accordingly, Applicants respectfully request that the Examiner reevaluate those references.

The next question is whether the data can be relied upon to carry out the claimed methods. In this regard, the Examiner appears to be questioning the predictive value of the mouse model used by Applicants to obtain the data. Applicants respectfully submit that the state of the art and the evidence presented before the Examiner are sufficient to establish such predictive value of the mouse model. Again, Applicants are not relying on the data obtained with the mouse model as an absolute prediction as to whether metastasis will or will not develop

in human patients. Rather, the data are highly valuable and relevant in *evaluating the risk* of developing a metastatic condition in human patients. Applicants submitted the abstracts of NCI-awarded grants and abstracts of publications by AntiCancer, Inc., to support the position that mouse models are highly valuable and useful in conducting research and obtaining data relevant for human cancers.

With respect to the conflicting prior art references related to correlation of fibronectin expression level with metastasis, or lack thereof, Applicants reiterate the fact that the prior art references relied on low-sensitivity detection methods such as immnohistochemistry and immunostaining to determine the level of fibronectin in their samples. In contrast, the instant application provides data obtained with highly sensitive microarray technology combined with RNAse protection assays and evaluated based on a rigorous standard. For example, the selection criterion was quoted above, and moreover, the specification provides:

> Three genes, fibronectin, rhoC, and thymosin β4, were expressed at higher levels in all three metastases selected from both the human A375 and mouse B16 cell lines, suggesting that their altered expression may be important for tumor metastasis. Enhanced expression of these three genes in the pulmonary metastases was confirmed by RNAse protection.

Page 30, lines 25-29 of the specification. Accordingly, Applicants submit that the conflicting prior art references only reflect the deficiencies on their part and do not render the data in the present application unreliable.

In sum, Applicants respectfully request that the Examiner reconsider and withdraw the rejections, particularly in view of the amended preamble in independent claims 14, 29, 38, and 40.

Rejection of Claims 12, 14, 17, 19, and 36-39 Under 35 U.S.C. § 102(b)

Claims 12, 14, 17, 19, and 36-39 stand rejected under 35 U.S.C. § 102(b) as allegedly unpatentable over Friedman et al.

As the Examiner has stated, Friedman et al. teach the association of greater expression level of TGFβ1 with metastatic cancer (as compared to non-metastatic cancer). Friedman et al. also teach that the expression of TGFβ2 or TGFβ3 correlate with disease progression to a lesser extent as compared to TGFβ1, and do not teach or suggest any other members of the TGFβ

super family. Applicants have amended claims 14 and 38 to specify the TGFβ super family gene product as that of the nucleic acid as represented by GenBank Accession No. AB000584, which amendment is supported by the specification as filed, for example, Table 2 of the specification. Accordingly, Applicants respectfully submit that Friedman et al. does not teach or suggest claims 14 and 38 as amended, and claim 39 which depends from claim 38. Therefore, the currently pending claims are patentable over Friedman et al.

Rejection of Claims 36-40 and 42 [sic] Under 35 U.S.C. §103(a)

Claims 36-40 and 42 [sic] stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Christensen et al. (Cancer Research 1988). Again, Applicants believe that the Examiner intended to reject claims 36-41.

For Christensen et al. to render the claimed invention obvious, it must, taken together with what was known in the prior art, teach or suggest every element of the claims at issue. Further, the state of the prior art must be such that it would have motivated a person having ordinary skill in the art to modify Christensen et al. to arrive at the claimed invention. Finally, there must also have been a reasonable expectation of success in achieving the claimed invention by modifying Christensen et al.

Applicants agree with the Examiner that the prior art was unpredictable as to the correlation (or lack thereof) of fibronectin expression level with metastasis potential of cancer cells. Applicants also provided further prior art references to the Examiner to demonstrate the unpredictable state of the prior art. However, precisely because of such unpredictability, Applicants maintain that the prior art would not have motivated one of ordinary skill in the art to modify Christensen et al. to carry out the claimed methods. Such unpredictability renders it unreasonable for one of ordinary skill in the art to have expected that, by modifying Christensen et al., one could have achieved the claimed invention.

Accordingly, Applicants respectfully submit that the pending claims are not obvious over Christensen et al. and request that the Examiner reconsider and withdraw the rejection.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in condition for immediate allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (617) 951-7000.

If any fee is due, please charge our **Deposit Account No. 18-1945**, from which the undersigned is authorized to draw under **Order No. WIBL-P01-534**.

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Respectfully submitted,

By _____

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